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# SIGNS OF COGNITIVE DYSFUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS IN CONDITIONS OF COVID-19

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**Annotation.** At the stage of new infections that are conquering the whole world, in particular with the COVID-19 pandemic worldwide, first identified at the end of 2019 in the People's Republic of China (PRC), in the city of Wuhan (Hubei province), it has been proven that it affects not only the brain and spinal cord, but also other organs, and the system, in connection with which an in-depth study is still underway, the development of new diagnostic tools, treatment and prevention of its complications. The aim of the study was to study cognitive functions in patients with multiple sclerosis in conditions of COVID-19 (infected with SARS-CoV-2). 42 patients with multiple sclerosis were studied, of whom 24 (57.1%) suffered COVID-19 of varying severity (group 1, comparative), and 18 (42.9%) remained intact (group 2, main). All patients underwent PCR analysis confirming infection with SARS-CoV-2, a study of C-reactive protein (CRP), ESR, white blood cell count, D-demir, urea and creatinine in venous blood. Cognitive impairment (CN) developed not only in patients with multiple sclerosis infected with coronavirus infection, but also in similar patients without COVID-19 infection. More extensive neuropsychological testing and analysis of the relationship between inflammatory markers (ESR, blood leukocytes, CRP) and CN were performed. The analyses were compared retrospectively and prospectively, 10-12 days after infection, at the stage of recovery. The presence of coronavirus pathology in patients with multiple sclerosis led to an aggravation of the clinical picture of the disease, mutually burdening each other, with a significant impact on the quality of life, the development of disability, through motor, somatosensory, visual, cognitive and neuropsychic disorders.

Relevance. The neuropathological process of multiple sclerosis (MS) is characterized by the appearance of pathological multifocal foci of demyelination with loss of oligodendrocytes and scarring of astroglia, inflammation and gliosis of varying severity, partial preservation of axons located in the optic nerves, spinal cord, brain stem, cerebellum, as well as in the juxtacortical and periventricular sections of the white matter of the brain [1; 7; 28]. In addition, demyelinated foci can also be found in the corpus callosum and cortical gray matter, i.e. The lesion covers a wider range of CNS structures, with progressive loss of brain volume. Inflammatory cortical demyelination was detected in 38% of patients according to MRI of the brain, confirmed by biopsy of cases of early MS [1; 4]. At later stages, axons are affected, thus, along with certain symptoms, the disease has a very variable rate and many atypical forms [17; 22].

According to etiology, the US National Center for Biotechnology Information has identified a number of factors for the development of MS: genetic, smoking, vitamin D deficiency, exposure to Epstein-Barr virus at an early age, high salt content in food, poor ecology [2; 6; 25]. Scientists at the University of California (San Francisco, PNAS-2020) have announced another possible reason - the presence of bacteria in the intestine, which cause cells of the immune system to harm the membrane of brain neurons [11; 27]. As can be seen, in relation to the etiology of MS, it is impossible to indicate certain factors, however, the most common hypothesis suggests an inflammatory onset of the disease involving the immune system, which is characterized by the appearance of autoreactive lymphocytes, activation of neuroglia and chronic neurodegeneration [3; 6]. Also, the non-immune, non-inflammatory origin of the disease suggests a genetically determined degenerative process of neuroglia [2; 7; 10].

Study of epidemiological analysis According to the US National Center for Biotechnology Information, 2.5 million people have been diagnosed with multiple sclerosis (MS) worldwide. It is diagnosed three times more often in women, the age of patients varies from 20 to 40 years [3; 5]. Young people under the age of 18 suffer from this disease in up to 10% of cases [9; 24]. Among disorders of the central nervous system, MS is the most common cause of permanent disability in young people. A systematic review of 28 epidemiological studies showed that from 1955 to 2000, the estimated ratio of MS incidence among women and men increased from 1.4:1 to 2.3:1, i.e., the incidence of MS is increasing in women for an unknown reason. It is observed that the disease is most often detected in the population of the Orkney Islands (northeast of Scotland), North America, Northern Europe, South Australia and southern New Zealand, according to the same data, cases of multiple sclerosis are detected 10-20 times less often in tropical countries. The prevalence of cognitive impairment in MS ranges from 40% to 70%. Studies have shown that [8; 11] in MS, physical symptoms of the disease are not an accurate predictor of cognitive impairment, i.e. patients suffering from severe physical symptoms may have fewer complaints of cognitive impairment or, conversely, patients with severe cognitive problems may have fewer physical symptoms [4; 21]. Attention, memory, visual abilities, information processing speed and executive functions among cognitive abilities may be most involved in patients with MS [9; 14]. As can be seen, cognitive dysfunction in MS can be a problem that leads to maladaptation of patients.

Currently, at the stage of new infections that are conquering the whole world, in particular with the COVID-19 pandemic worldwide, first identified at the end of 2019 in the People's Republic of China (PRC), in the city of Wuhan (Hubei province), it has been proven that they affect not only the brain and spinal cord, but also and other organs and systems, in connection with which an in-depth study and development of new means of diagnosis, treatment and prevention of its complications are still ongoing [6; 20]. In addition to the physical, social and economic problems with COVID-19, many people suffer from psychological problems – anxiety, depression, insomnia, despair and fear of infection [9, 10]. Despite the possible side effects of drugs, exacerbation of the clinical course of the underlying disease (MS) in coronavirus infection, it has been proven in the experience of managing patients with coronavirus infection, patients with multiple sclerosis are more afraid to catch COVID-19, which is actually the psychological side of the development of worsening consequences [23; 26].

It has been proven that a group of human respiratory coronaviruses (HCoV) are neurotropic, and can penetrate into the brain and cerebrospinal fluid, however, they are detected in the cerebrospinal fluid a week after infection [4; 13]. However, in some studies, the results of the analysis of cerebrospinal fluid for SARS-CoV-2 by polymerase chain reaction in patients with COVID-19 and neurological manifestations were negative [10, 12]. According to L. Mao et al. 36.4% of patients with COVID-19 have neurological symptoms and damage to the central (CNS) and peripheral nervous system (PNS) by COVID-19 viral invasion have a severe clinical course and serious consequences [13; 16], up to the development of encephalitis, meningitis, impaired sense of smell and taste, mono- and polyneuropathy, confusion and epileptic seizures [18, 6]. With a different etiology, such diseases, or rather complications, are considered as more studied conditions, and are treated according to a certain scheme, without delaying either time or days. However, the pathogenesis of the development of such conditions in COVID-19 remains far from understood, especially considering that it is also a risk factor for the development of cerebrovascular diseases: stroke and venous sinus thrombosis [7; 16; 24]. Moreover, COVID-19 increases the risk of encephalopathy, cerebral microbleeds, autoimmune diseases, including Guillain–Barre syndrome, exacerbates and worsens the condition of patients with multiple sclerosis and similar diseases [12; 19]. There are studies proving an increased risk of neurocognitive disorders in COVID-19 infected by direct invasion of the virus into the central nervous system, which is carried out in two ways: hematogenous, through damage to the blood-brain barrier (BBB) with high cytokine levels, or neuronal, through peripheral neurons to the central nervous system. In severe COVID, brain hypoxia due to lung damage also plays an important role [11; 15]. Relying on these data, the

study of cognitive function in patients with multiple sclerosis who have undergone COVID-19 is an urgent and not fully understood problem, according to various data, which are evaluated ambiguously and require further monitoring, especially for choosing the right patient management tactics.

Based on such considerations, the purpose of our study was to study the state of cognitive functions in patients with multiple sclerosis in conditions of COVID-19 (infected with SARS-CoV-2).

Research materials and methods. 42 patients with multiple sclerosis were studied, of whom 24 (57.1%) suffered COVID-19 of varying severity (group 1, comparative), and 18 (42.9%) remained intact (group 2, main). According to the severity of the condition of patients who underwent COVID-19, a mild course was noted in 6 (14.3%), moderate severity in 11 (26.2%) and 7 (16.7%) patients, a severe clinical course of coronavirus infection, up to the development of COVID pneumonia. The average age group in patients with MS who suffered from coronavirus pathology was equal to 41.2 ±2.7 years; In group 2, this age was on average 39.6±2.6 years old. As can be seen, there was no significant difference between the age category in the examined groups. An MRI examination of the brain with contrast enhancement and the spinal cord without contrast was performed, a neurological examination, a thorough history collection, and a study of cognitive function using cognitive scales. All patients underwent PCR analysis confirming infection with SARS-CoV-2, a study of C-reactive protein (CRP), ESR, white blood cell count, D-demir, urea and creatinine in venous blood. In the case of a positive PCR analysis, patients continued to be examined 10-12 days after the improvement of their clinical condition on their own and the negative result of repeated PCR. All the studied patients received written consent to conduct this analysis.

Results and discussion. Cognitive impairment (CN) developed not only in patients with multiple sclerosis infected with coronavirus infection, but also in similar patients without COVID-19 infection. More extensive neuropsychological testing and analysis of the relationship between inflammatory markers (ESR, blood leukocytes, CRP) and CN were performed. The analyses were compared retrospectively and prospectively, as mentioned above, 10-12 days after infection, in the recovery stage. Concentration and stability of attention were assessed by the Bourdon "proof-reading test", in which a pre-prepared form with different randomly arranged letters was set, and one letter was selected, which the patient had to mark within 5 minutes, the faster and more of this letter in whole rows the patient chose, the more stable and voluminous attention was considered, and concentration of attention was considered as the norm. The interpretation of the results was carried out in comparison with the norm of an adult: the volume was 850 characters or higher, the concentration was 5 errors or less. The speed of thinking was determined by performing its indicative and operational components. To do this, special forms were prepared with words in which letters were missing, and within 3 minutes patients had to identify the missing letters, and the procedure began on a signal. The results were evaluated by the number of correctly composed words. The indicator of the speed of thinking and mobility of nervous processes (NP) was considered as: less than 20 words out of 40 – low speed of thinking and mobility of NP; 21-30 words – average speed of thinking and mobility of NP; 31 or more words – high speed of thinking and mobility of NP. According to the method of A.R. Luria, the "memorization of 10 words" test was used to assess the state of memory, voluntary attention, as well as to study the dynamics of the course of cognitive function in multiple sclerosis and layering in these patients with coronavirus pathology. For the test, they read a few words and asked the patient to repeat them. the words were in any order, so it was repeated 5-6 times, then, after 1 hour, they were asked to repeat all the words without first reading them out. A protocol was filled out at each stage of the study. A cross was placed under each reproduced word in the line that corresponds to the number of the attempt, and the "superfluous" called word was fixed in the appropriate column. An hour later, the remembered words were recorded in the protocol in circles. If the subject reproduced fewer and fewer words, replaced them with others, or often reproduced one word several times, then this was assessed as a decrease in memory and the presence of absent-mindedness.

Compared with the 1st comparison group, patients who underwent COVID-19 (the 2nd main group) performed worse on the Bourdon proofreading test, speed of thinking and mobility of nervous processes and the 10-word memorization test. It should be noted that in the 1st group of patients there were also significant differences in concentration and stability of attention, memory and thinking compared with healthy people ($P<0.05$), however, this difference between the 1st and 2nd groups was more significant ($P<0.001$). In addition, a direct correlation was found between the level of C-reactive protein and the weakness of concentration and attention stability ($r=2.18$) and the speed of thinking ($r=3.17$). Cognitive impairments detected since the diagnosis of multiple sclerosis progressed slowly, as in the classical understanding of it [6, 7], however, when infected with COVID-19, their rapid progression was noted, reaching a pronounced degree. Moreover, a decrease in concentration and stability of attention, information processing speed, thinking, and short-term memory significantly affected spatial gnosis, understanding of complex speech syntactic structures, and planning functions. This led to significant maladaptation of the patient and dramatically reduced the effectiveness of his daily activities. Emotional lability, tearfulness, fear of premature death, depression, and a pronounced vegetative reaction with the presence of severe tremor in the distal parts of the upper and lower extremities were also detected when patients with multiple sclerosis were infected with coronavirus infection. According to laboratory data, in group 2, signs of systemic inflammation, a "cytokine storm", coagulopathy were noted, the level of C-reactive protein sharply increased, which aggravated the clinical course of multiple sclerosis, became the cause and potential mechanism of the development of CN in COVID-19.

During an MRI examination of the brain with contrast enhancement, foci of encephalomalacia in the hemispheres of the cerebrum and cerebellum, in the periventricular region and semioval areas were determined in the images obtained centers with signs of edema at the anterior horn, local foci in the form of pathological accumulation in the hemispheres of the hemispheres and in the area of the basal nuclei. Foci of encephalomalacia were also found in segments of the spinal cord in the form of merging waves.

Patient M., a 19-year-old girl, a university student, fell ill with COVID-19 in May 2020 against the background of complete health (confirmed by the results of a study by polymerase chain reaction (PCR) of a smear from the mouth and nasopharynx. Computed tomography (CT) denies the presence of pathology in the lungs). The general condition was of moderate severity, blood oxygen saturation was 96-97%, oxygen support was not required. In the blood, an increase in the level of C-reactive protein was observed to 78.2 mg/l (at a rate of 0-5 mg/l), interleukin 6 – to 184.6 pg/ml (at a rate of 0-7 pg/ml), ESR – up to 42 mm/h. Coagulogram – without significant changes.

In July 2020, he gets excessively stressed, and moves from one city to another, unwittingly (almost the same climatic conditions, but different living conditions). In August 2020, parents noted impaired coordination of movements, slight nasal twang, weakness of the left extremities according to the hemitype, irritability, tearfulness, excessive lability, impaired night sleep, decreased memory and information processing speed. The patient receives treatment at home several times, periodically taking conservative therapy, while not observing bed rest, rest regime. Within 3 months, the symptoms disappear completely. However, in 2021, in September, a second exacerbation occurs, more severe than the first. In the neurological status, horizontal nystagmus, nasal speech, impaired coordination of movements, shakiness when walking are noted. Due to insomnia during the last 10-15 days, he has noted the appearance of anxiety and fear of death closer to evening time. The proboscis reflex, the revival of the mandibular reflex, the revival of tendon reflexes with hyperreflexion on the left hemitype were found in the neurological status. According to the Montreal Cognitive Assessment Scale (MoSA), the patient scored 22 points (with a norm of ≥26 points). In the test for memorizing ten words, the patient was able to reproduce 6 words out of ten; there was a decrease in concentration and stability of attention, speed of thinking and information processing. Mild anxiety according to the Generalized Anxiety Disorder test-7, GAD-7 and mild depression according to the Patient

Health Questionnaire test-9 (PHQ-9) were revealed. Treatment according to the generally accepted treatment regimen for multiple sclerosis is recommended. MRI of the brain shows single foci of encephalomalacia up to 5-6 mm in size, sometimes merging in the hemispheres of the brain and larger 2 foci in the hemispheres of the cerebellum.

As can be seen, a young girl, against the background of COVID-19 infection and stress, has an autoimmune reaction of the body with the development of severe pathology, such as multiple sclerosis, and a picture of cognitive deficit, which requires careful monitoring, periodic prevention of exacerbation and rehabilitation measures to prolong the period of remission, as well as to prevent the development of disability.

Thus, summarizing the scientific observation, we can conclude:

1. Multiple sclerosis, which is one of the severe diseases of the central nervous system leads to the development of cognitive dysfunction, infection of patients with COVID-19 multiple sclerosis, which has proven the originality and severity of clinical manifestations, in part related to the pathology of the central nervous system, may be the cause of exacerbation of cognitive deficits of an irreversible nature;

2. The presence of coronavirus pathology in patients with multiple sclerosis undoubtedly leads to an aggravation of the clinical picture of the disease, mutually burdening each other, with a significant impact on the quality of life, the development of disability, through motor, somatosensory, visual, cognitive and neuropsychic disorders.

3. COVID-19 can be an independent source of the development of autoimmune diseases, in particular multiple sclerosis, which requires a timely approach and early therapy.

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